1,015,800

PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Improvements in or relating to Nicotinic Acid Derivatives

We, FUJISAWA PHARMACEUTICAL CO., LTD., a Japanese Body Corporate, of 3, Doshomachi 4-Chome, Osaka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new and useful nicotinic acid derivatives, and more particularly to tri- or tetra-nicotinic acid esters of glucuronic acid derivatives and to a process for their preparation.

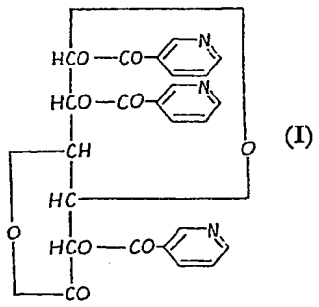
Nicotinic acid is known to possess an anti-pellagra action as a vitamin. It is also effective in dilating the peripheral vascular bed, in lowering cholesterol blood levels and in enhancing fibrinolytic activity, and accordingly nicotinic acid has been used for the treatment of diseases due to disturbances of peripheral circulation, arteriosclerosis, etc. However, these conditions have a tendency to become chronic, requiring long-term therapy with nicotinic acid. In addition, the action of nicotinic acid is only transient, and frequently causes such side effects as facial flush, and formication (skin irritation).

It has also been recognised that D-glucuronic acid and its lactone (glucurone) have beneficial effect in rheumatoid arthritis, fibrositis, and neuritis.

It is an object of this invention to provide agents which are effective for the treatment of diseases due to disorders of e.g. peripheral circulation, and arteriosclerosis.

It is another object to provide such agents which do not share the disadvantages of nicotinic acid.

The compounds of this invention are nicotinic acid esters of a lactone ester or amide of glucuronic acid and possess one of the following two structural formulae:—



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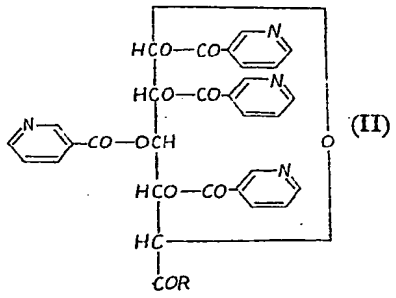


(II)

wherein R represents an alkoxy radical or an amino radical.

The compounds of this invention may be prepared by reacting glucuronic acid, an inorganic or ammonium salt thereof, glucuronolactone, an alkyl ester of glucuronic acid or glucuronamide with nicotinic acid or a functional derivative thereof.

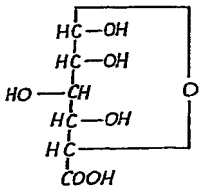
Functional derivatives of nicotinic acid which may be used in this invention are those derivatives which will acylate the hydroxy radicals of the other reactant, such as nicotinoyl halides, nicotinic anhydride and a mixed anhydride of nicotinic acid with various kinds of organic or inorganic acids.

As mentioned above, the derivatives of

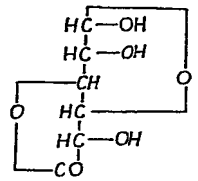
[Price 4s. 6d.]

glucuronic acid to be used as the starting materials in this invention are glucuronolactone, alkyl esters of glucuronic acid, preferably lower alkyl esters, glucuronamide and salts of glucuronic acid with, for example, alkali metals, alkaline earth metals, and ammonia. In the reaction of this invention all of the free hydroxy radicals of glucuronic acid or its derivatives are esterified with nicotinic acid or its reactive derivatives.

It is generally believed that the naturally occurring glucuronic acid has the following structure which is a six membered lactonol ring connecting the positions 1 and 5;



and glucuronic acid and its salts readily undergo rearrangement in solution to form glucuronolactone which has two five membered lactonol ring as follows:



Accordingly, when using glucuronolactone, glucuronic acid or its salt as the starting material, glucuronolactone 1,2,5-trinicotinate will be obtained. When using glucuronic acid ester or glucuronamide a tetranicotinate of the starting material will be obtained. When using an acid halide or an acid anhydride as the functional derivative of nicotinic acid, the reaction is preferably carried out in the presence of a base such as alkali metal carbonate, alkali metal bicarbonate, trimethylamine, triethylamine, dimethylaminoacetamide, dimethylformamide, dimethylaniline, or pyridine.

When using the free acid, it is advantageous to carry out the reaction in the presence of a condensing agent such as boron fluoride, N,N^1-carbonyl-diimidazole, N,N^1 - carbonyldi - (2-methyl)-imidazole and *p*-toluene sulphonic acid.

The reaction is usually carried out in a solvent, a few examples being aromatic hydrocarbons such as benzene, toluene, and xylene, or inert solvents such as dioxane. When using a base which is a liquid, this can also serve as the solvent. A suitable solvent should be selected with due consideration of the reaction conditions including the desired reaction temperature. The reaction may be carried out at various temperatures, without any particular limitation.

If desired, the compounds obtained in accordance with this invention may be converted to their acid addition salts by well-known methods. Preferred examples of suitable acids are hydrochloric acid, sulphuric acid and picric acid.

The compounds of this invention are useful in the treatment of diseases due to disturbances of peripheral circulation and arteriosclerosis, and are superior to nicotinic acid in their absorbability and long-lasting activity as well as in lesser manifestation of side effects.

This invention includes within its scope pharmaceutical compositions which comprise one or more of the compounds of this invention together with a pharmaceutically-acceptable non-toxic liquid, solid or pasty carrier.

Solid compositions for oral administration include tablets, pills, dispersible powder and granules. In such solid compositions one or more of the active compounds are admixed with one inert diluent, such as potato starch, lactose or calcium carbonate, and further additional substances, e.g. lubricating substances may be added. Liquid compositions for oral administration include pharmaceutically acceptable solutions, and suspensions, containing inert diluents commonly used in the art. The compositions for oral administration also include capsules of absorbable material such as gelatin containing one or more of the active compounds with or without the addition of diluents or excipients.

The following examples are given for the purpose of illustrating the invention and the manner in which it may be carried into effect:—

EXAMPLE 1

The mixture of 4.4 g of nicotinic acid and 4.5 g of thionyl chloride in 20 cc of toluene is heated in the presence of 0.26 g. of dimethylformamide under reflux for 2 hours to prepare a toluene solution of nicotinoyl chloride. Precautions are taken to exclude water from this solution, which is cooled to 0°C, and to which is added 1.76 g. of D-glucofuranurono-6,3-lactone in 10 cc. of pyridine while stirring and the mixture is stirred at 0°—50°C for 4 hours. To the reaction mixture is added 100 cc of chloroform and the mixture is washed with water and then, after drying, decolourised. The solvent is distilled off to obtain 4.0 g. of a brown oily substance.

This substance is dissolved in 40 cc of chloroform and to this solution is added about 1.5 cc of ether and the resultant mixture is allowed to stand to yield 1.9 g of D-glucofuranurono-6,3-lactone 1,2,5-trinicotinate as white crystals having m.p. (dec.), 171—172°C.

Analysis: Calculated for $C_{24}H_{17}O_9N_3$
C 58.66, H 3.49, N 8.55
Found C 58.46, H 3.62, N 8.50.

This substance is dissolved in methanol and allowed to react with a methanol solution of picric acid to obtain the picrate having m.p. 145—152°C and Ultra-Violet Absorption Spectrum $\lambda_{max}^{methanol}$ 360 mμ (ε 42.500).

Analysis: Calculated for $C_{42}H_{26}O_{30}N_{12}$
C 42.80, H 2.22, N 14.26
Found C 42.79, H 2.71, N 14.03.

Example 2

To 9.1 g of nicotinic anhydride in 50 cc. of pyridine, which is cooled to 0°C, is added 0.85 g. of D-glucofuranurono-6,3-lactone in 20 cc of pyridine while taking precautions to exclude water, and the mixture is stirred at 5—15°C for 7 hours. The reaction mixture is allowed to stand overnight in a cold place and filtered. The residue is washed with chloroform. The filtrate and the washings are combined, washed with water and then decolourised after drying. The solvent is distilled off to produce 1.9 g. of a brown oily precipitate, which is recrystallised from a mixture of chloroform and ether to yield 0.8 g of D-glucofuranurono-6,3-lactone 1,2,5-trinicotinate having m.p. (dec.), 175—176°C, which shows no depression of melting point on admixture with the product of Example 1.

Example 3

A mixture of 7.38 g. of nicotinic acid and 7.4 g. of thionyl chloride in 80 cc of toluene is heated in the presence of 4 cc of dimethylformamide under reflux for 3 hours to prepare a solution of nicotinoyl chloride. To this cool solution are added 30 cc. of pyridine and then 2.0 g of sodium glucopyranuronate, and the mixture stirred at 40°C for 3 hours. The reaction mixture is washed with water, dried and then decolourised, after which the solvent is distilled under reduced pressure. The residue is recrystallized from a mixture of chloroform and ether to obtain 1.0 g. of gluocofuranurono-6,3-lactone 1,2,5-trinicotinate having m.p. (dec.) 174—175°C.

Analysis: Calculated for $C_{24}H_{17}O_9N_3$
C 58.66, H 3.49, N 8.55
Found C 58.22, H 3.73, N 8.13.

Example 4

A mixture of 1.5 g of sodium glucopyranuronate and 7.5 g of nicotinic anhydride in 50 cc of pyridine is stirred at 40°C for 4 hours. After allowing to stand overnight, the precipitated nicotinic acid is removed from the reaction mixture by filtration and the residue is washed with ethyl acetate. The filtrate and the washings are combined and, after drying, the solvent is distilled off under reduced pressure. The remaining orange-yellow gummy substance is dissolved in chloroform and decolourised, after which ether is added to this solution and 1.2 g of glucofuranurono-6,3-lactone 1,2,5-trinicotinate having m.p. (dec.) 171—175°C is crystallised from the chloroform/ether solution.

Example 5

A mixture of 6.7 g of nicotinic acid and 6.7 g of thionyl chloride in 30 cc of toluene is heated under reflux to obtain a solution of nicotinoyl chloride. To this solution are added 2.4 g. of barium glucopyranuronate and 30 cc of pyridine, and the mixture stirred at 0°C for 5 hours and at room temperature for a further hour. The reaction mixture is filtered and the residue washed with chloroform. The filtrate and the washings are combined, washed with water, dried, and then decolourised, after which the solvent is distilled off under reduced pressure and the residue is dissolved in chloroform. To this solution is added ether and glucofuranurono-6,3-lactone 1,2,5-trinicotinate having m.p. (dec.), 174—175°C.

Analysis: Calculated for $C_{24}H_{17}O_9N_3.1/2H_2O$
C 57.60, H 3.63, N 8.40
Found C 57.42, H 3.63, N 8.17.

EXAMPLE 6

To 6.8 g of nicotinic anhydride in 40 cc of pyridine is added 0.95 g of methyl D-glucopyranuronate and the mixture stirred at 10—15°C for 3 hours with exclusion of moisture. The reaction mixture is filtered and the residue is washed with chloroform. The filtrate and the washings are joined, washed, dried, and then decolourised, after which the solvent is distilled off. The residue is dissolved in chloroform and an insoluble substance is separated. The solvent is distilled off under reduced pressure to yield 1.8 g of methyl D-glucopyranuronate 1,2,3,4-tetranicotinate as a gummy substance.

Ultra-Violet Absorption Spectrum:

$\lambda_{max}^{methanol}$ 264 mμ (ε 9500)

To this substance dissolved in methanol is added a methanol solution of picric acid to prepare the picrate, which is recrystallised from methanol to obtain crystals having m.p. 125—128°C.

Analysis: Calculated for $C_{55}H_{36}O_{31}N_{16}$
C 42.75, H 2.54, N 14.57.
Found C 42.48, H 2.82, N 14.28.

Ultra-Violet Absorption Spectrum:

$\lambda_{max}^{methanol}$ 361 mμ (ε 59,000)

EXAMPLE 7

To 5.7 g of nicotinic anhydride in 30 cc of pyridine is added 1.0 g. of D-glucopyranuronamide and the mixture stirred at 10—20°C for 6 hours with exclusion of moisture. After allowing it to stand overnight, the reaction mixture is filtered and the residue washed with chloroform. The filtrate and the washings are joined, washed with a 10% aqueous sodium carbonate several times, then with water and dried. The solvent is distilled off under reduced pressure to yield 1.3 g. of a brown gummy substance, which is dissolved in 40 cc of chloroform, decolourised, and then evaporated to about 1/3 the volume. To this solution is added ether and the mixture allowed to stand, with the result that 1.1 g of D-glucopyranuronamide 1,2,3,4-tetranicotinate as a pale yellow fine powder (hygroscopic) having m.p. (dec.) 116—120°C is crystallised from the mixture.

Analysis: Calculated for $C_{30}H_{23}O_{10}N_5 \cdot H_2O$
C 57.05, H 3.99, N 11.09
Found C 56.94, H 4.17, N 11.29.

Ultra-Violet Absorption Spectrum:

$\lambda_{max}^{95\%\ ethanol}$ 264 mμ (ε 11,167)

$[\alpha_D]^{20} = +78.6$ (C=1.1%, 95% ethanol).

Infrared Absorption Spectrum: ("Nujol" mull) cm^{-1}; "Nujol" is a registered trade mark.

3300 broad (γ_{N-H}^{amine} plus $\gamma_{O-H}^{cryst.H_2O}$),

$\gamma_{C=O}^{ester}$ 1735, $\gamma_{C=O}^{amide}$ 1690, $\gamma_{C=O}^{ester}$ 1270 and 1105,

$\omega_{C=C}^{pyridine\ nucleus}$ 1595, $\delta_{C-H}^{pyridine}$ 740 and 700.

EXAMPLE 8

A mixture of 4.6 g of nicotinic acid and 4.6 g of thionyl chloride is heated in 50 cc of toluene and 3 cc of dimethylformamide under reflux for 2 hours to prepare a solution of nicotinyl chloride. This solution is cooled at 0°C, added dropwise to 1.0 g of glucopyranuronamide in 50 cc of pyridine and 15 cc of dimethylformamide, with exclusion of moisture, and then stirred at 15°C for 2 hours. After allowing to stand overnight, the reaction mixture is filtered and the residue is washed with chloroform. The filtrate and the washings are joined, poured into water and the organic solvent layer is separated. The water layer is washed with chloroform and the washings added to the organic solvent layer. After washing with water and drying, the solvent is dis-

tilled off to yield 1.4 g of a brown gummy substance, which is dissolved in ethyl acetate and insoluble material is removed. To this solution is added ether and the resultant precipitate, which is collected by filtration, is dissolved in chloroform and decolourised. Ether is added to the solution and D-glucopyranuronamide 1,2,3,4 - tetranicotinate is crystallised from the chloroform/ether solution as a pale yellow fine powder (hygroscopic) having m.p. 109—122°C.

By means of Infrared spectroscopy, this is identified as the same substance as the sample obtained by Example 7.

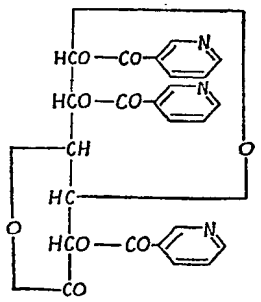
WHAT WE CLAIM IS:—

1. A process for the production of a nicotinic ester of a lactone ester or amide of glucuronic acid which comprises reacting nicotinic acid or a functional derivative thereof with glucuronic acid, an inorganic or ammonium salt thereof, glucuronolactone, an alkyl ester of glucuronic acid or glucuronamide.

2. A process according to claim 1 wherein the functional derivative of nicotinic acid is nicotinic anhydride or a nicotinyl halide and the reaction is carried out in the presence of a base.

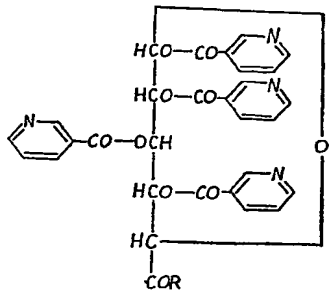
3. A process according to claim 2 wherein the base is an alkyl metal carbonate, an alkali metal bicarbonate, trimethylamine, triethylamine, dimethylaminoacetamide, dimethylformamide, dimethylaniline or pyridine.

4. D - glucofuranurono - 6,3-lactone - 1,2,5-trinicotinate having the formula:



and acid addition salts thereof.

5. A nicotinic acid ester of a lactone ester or amide of glucuronic acid having the formula:



wherein R represents an amino radical or an alkoxy radical, and acid addition salts thereof.

6. Methyl D - glucopyranuronate - 1,2,3,4-tetranicotinate and acid addition salts thereof.

7. D - glucopyranuronamide - 1,2,3,4 - tetranicotinate and acid addition salts thereof.

8. A pharmaceutical composition comprising, as the active ingredient, a nicotinic acid ester of a lactone ester or amide of glucuronic acid as claimed in any of claims 4 to 7 and a non-toxic, pharmaceutically acceptable carrier.

9. The process for the production of a nicotinic acid ester of a lactone ester or amide of glucuronic acid substantially as described with reference to any of Examples 1 to 8.

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Chartered Patent Agents,
Agents for the Applicants.

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